

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Ladner 7C-P	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US92/01501	International filing date (day/month/year) 28.02.92	Priority date (day/month/year) 01.03.91
International Patent Classification (IPC) or national classification and IPC C12N15/15		
Applicant Protein Engineering Corporation et al		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of <u>7</u> sheets. <input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings amended during international preliminary examination and/or containing rectifications made before this Authority. These annexes consist of a total of <u> / </u> sheets.
3.	This report contains indications and corresponding pages relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application

Date of submission of the demand 24.09.92	Date of completion of this report 21.06.93
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US 92/01501

I. Basis of the report

1. This report has been drawn up on the basis of:

- ☒ the international application as originally filed.
- ☐ the description, pages _____, as originally filed,
 pages _____, filed with the demand,
 pages _____, filed with the letter of _____,
 pages _____, filed with the letter of _____.
- ☐ the claims, No. _____, as originally filed,
 No. _____, as amended under Article 19,
 No. _____, filed with the demand,
 No. _____, filed with the letter of _____,
 No. _____, filed with the letter of _____.
- ☐ the drawings, sheets/fig. _____, as originally filed,
 sheets/fig. _____, filed with the demand,
 sheets/fig. _____, filed with the letter of _____,
 sheets/fig. _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of: pages: _____
 sheets of drawings/figures No.: _____.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box.

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US 92/01501

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	01 - 13	YES
	Claims		NO
Inventive Step (IS)	Claims	01 - 13	YES
	Claims		NO
Industrial Applicability (IA)	Claims	01 - 13	YES
	Claims		NO

2. CITATIONS AND EXPLANATIONS

Please, see separate sheet.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The International Preliminary Examining Authority has to issue a warning concerning a lack of unity of the present International Application (Rule 13, PCT).

The present application may be subdivided in the following groups of inventions:

- 1) inhibitors of human neutrophil elastase derived from BPTI or ITI - D1 (Claims 1 and 3, respectively).
- 2) inhibitors of human cathepsin G derived from BPTI (Claim 2).
- 3) inhibitors of human neutrophil elastase consisting of derivatized peptides (Claims 7 - 11).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US 92/01501

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims should be clear by themselves. However, Claims 1-2 contain internal denominations (Epi N..., Epi C...) meaningless for the person skilled in the art.

- 18/PCTIS
- 1). The present International Application relates to muteins of bovine pancreatic trypsin inhibitor (BPTI), inter-alpha-trypsininhibitor-D1 (ITI-D1) and other Kunitz domain-type inhibitors which have a high affinity for elastase and cathepsin G.

Furthermore, the present application also relates to derivatized peptides which bind elastase or cathepsin G, and more particularly to elastase-binding polypeptide (EpiNe) type human neutrophil elastase (hNE) inhibitors. Said inhibitors may be grouped into Class I, II, and III inhibitors (Fig. 8, 9, and 12 respectively).

- 2). The subject-matter of claim 1 relates to BPTI muteins having amino acid substitutions around the P1 region. With respect to claim 1, the closest prior art document is EP-A-0 307 592 (D1) which discloses BPTI variants. Since the specific amino acid combinations of the EpiNe... claimed in claim 1 and shown in Tables 207-208 of the present application are neither described nor suggested in D1, the subject-matter of claim 1 is novel (Art. 33 (2) PCT) and also involves an inventive step (Art. 33 (3) PCT).

The above comment also applies to claim 2, the subject-matter of which are inhibitors of human cathepsin G having amino acid (a.a.) substitutions around the P1 region (a.a. 15-19 and a.a. 39-42) of BPTI.

Claim 3 refers to inter-alpha-trypsininhibitor (ITI-D1) muteins. With respect to claim 3, the closest prior art document is EP-A-0 041 508 (D2).

Claim 3 differs from D2 in that amino acid substitutions in ITI (numbering according to D2) are disclosed for example in positions 22, 23, 25, 37, 39, and 40.

Having regard to the documents cited in the

International Search Report, the subject-matter of claim 3 is novel (Art. 33 (2) PCT). Since the above mentioned amino acid substitutions were neither disclosed nor suggested in D2, claim 3 also involves an inventive step (Art. 33 (3) PCT).

Claims 7-12 relate to derivatized peptides which are inhibitors of human neutrophil elastase.

With respect to said claims the closest prior art document is EP-A-0 195 212 (D3).

It appears that D3 neither discloses nor suggests the subject-matter of said claims, and, therefore, said claims seem to meet the requirements of Art. 33 (2) and (3) EPC.

The industrial applicability of claims 1-13 is acknowledged (Art. 33 (4) PCT).